

Drug Manufacturing

BEFORE PROMISING-LOOKING DRUG CANDIDATE REACHES THE CLINIC AND
GOES INTO FULL-SCALE PRODUCTION

- ▶ Please click the following link to have an idea of Drug Manufacturing.
- ▶ <https://www.bing.com/videos/search?q=drug+manufacturing&ru=%2fvideos%2fsearch%3fq%3ddrug%2bmanufacturing%26FORM%3dHDRSC3&view=detail&mid=484F97B1058F9709CB54484F97B1058F9709CB54&&FORM=VDRV RV>

- ▶ The drug has to be tested to ensure that it is safe and effective
- ▶ It involves preclinical and clinical trials covering -
 - ▶ Toxicity
 - ▶ Drug metabolism
 - ▶ Stability
 - ▶ Formulation and
 - ▶ Pharmacological tests
- ▶ Also Patenting and Legal Issues

Preclinical and clinical tests

- ▶ Toxicity test
- ▶ It starts with in vitro tests on -
- ▶ Genetically engineered cell cultures and/or
- ▶ Transgenic mice to examine any effects on cell reproduction
- ▶ Identify potential carcinogens

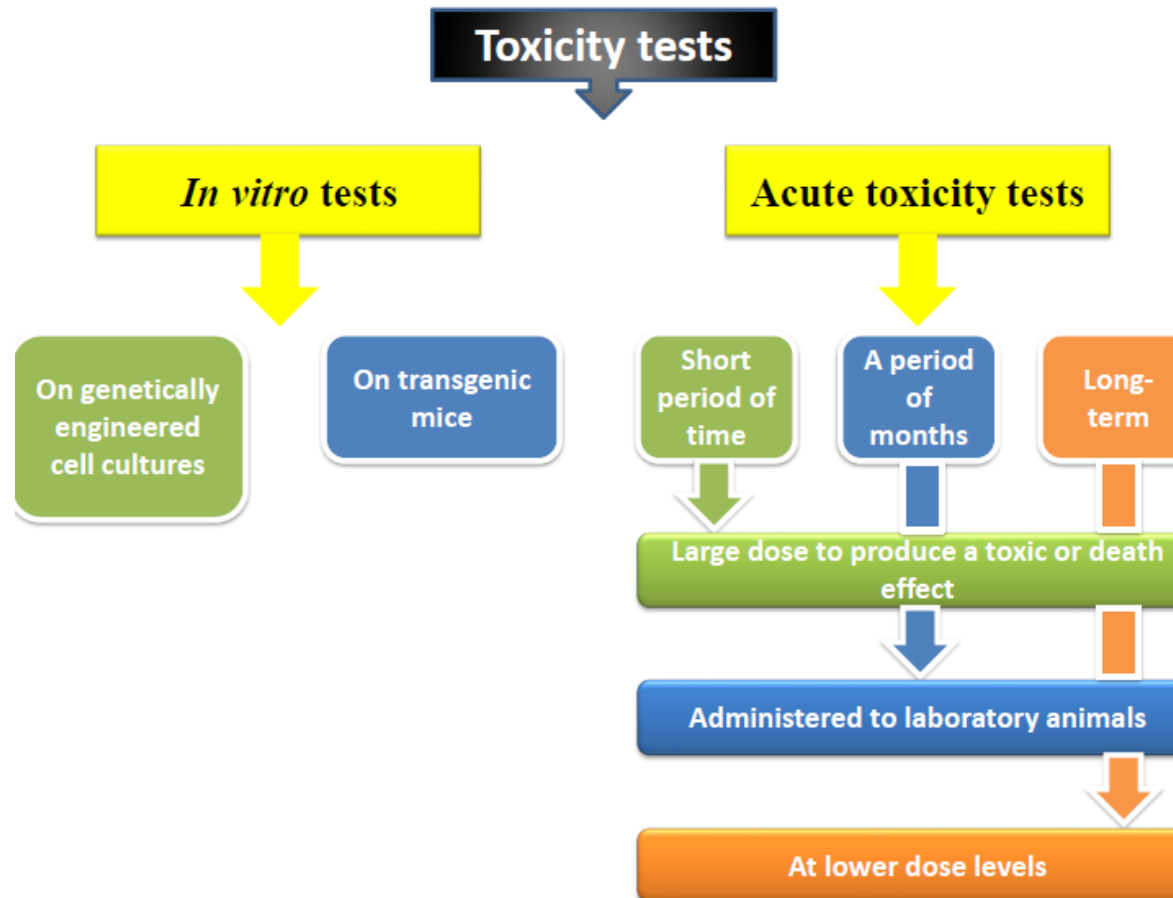
Preclinical and clinical tests

- ▶ The drug is tested for acute toxicity by
 - ▶ Administering sufficiently large doses in vivo
 - ▶ Producing a toxic effect or death over a short period of time
- ▶ Different animal species are used in the study and to test whether any particular organs are affected.
- ▶ Acute toxicity takes place over a period of months at a dose level expected to cause toxicity but not death.

Preclinical and clinical tests

- ▶ Blood and urine samples are analysed over that period and then animals are killed to analyse tissues by pathologists for any sign of cell damage or cancer (tumor).
- ▶ Long-term toxicology tests are carried out over a period of years
- ▶ At low dose levels to test the drug
- ▶ Chronic toxic effects
- ▶ Carcinogenicity
- ▶ Special toxicology
- ▶ Mutagenicity
- ▶ Reproduction abnormalities

Preclinical and clinical tests



Preclinical and clinical tests

- ▶ The toxicity of a drug used to be measured by its LD_{50} value (lethal dose).
- ▶ The lethal dose required to kill 50% of a group of animals.
- ▶ ED_{50} (effect dose)
- ▶ The effect dose required to produce the desired effect in 50% of test animals.
- ▶ The ratio of $LD_{50} : ED_{50}$ known as
the therapeutic ratio or therapeutic index

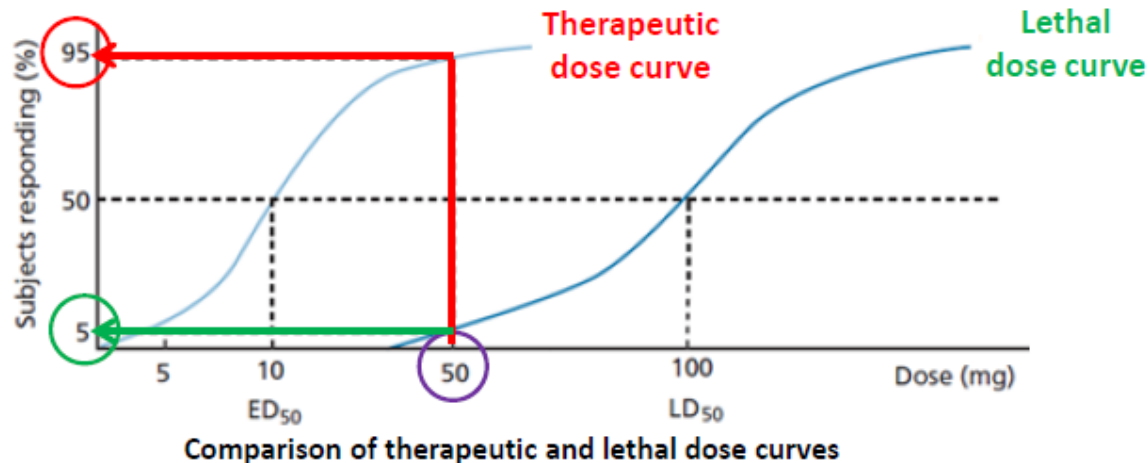
Preclinical and clinical tests

- ▶ The therapeutic ratio of 10 indicates an $LD_{50} : ED_{50}$ ratio of 10:1.
- ▶ It means a 10-fold increase in the ED_{50} dose would result in a 50% of death rate.
- ▶ The dose-response curves for a drug's therapeutic and lethal effects can be compared to determine whether the therapeutic ratio is safe or not.

Preclinical and clinical tests

- ▶ It shows the therapeutic and lethal dose-response curves for a sedative (鎮靜劑).
- ▶ A 50 mg dose of the drug can act as a sedative for 95% of the test animals but can be lethal for 5%.

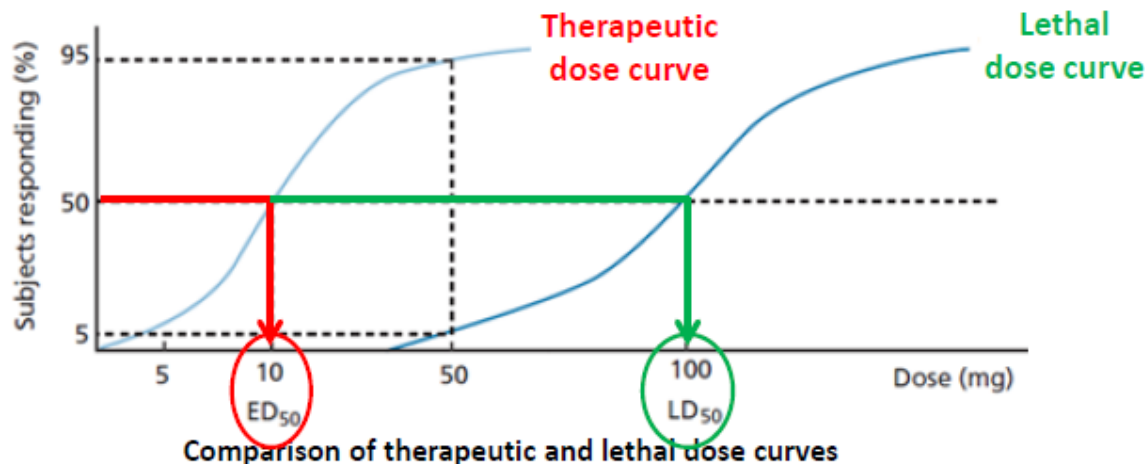
Graham, P. L. *An Introduction to Medicinal Chemistry*



Preclinical and clinical tests

- ▶ ED_{50} (effect dose) is 10 mg
- ▶ LD_{50} (lethal dose) is 100 mg
- ▶ Therapeutic ratio is $LD_{50} : ED_{50}$ 100:10 i.e. 10:1

Graham, P. L. *An Introduction to Medicinal Chemistry*



Preclinical and clinical tests

- ▶ A better measure of a drug's safety is to measure the ratio of the lethal dose for 1% of the population to the effective dose for 99% of the population.
- ▶ LD values and the therapeutic ratios are not the best indicators of a drug's toxicity as they fail to register any non-lethal or long-term toxic effects.
- ▶ Toxicity test should include a large variety of different
- ▶ In vitro tests and
- ▶ In vivo tests

Preclinical and clinical tests

- ▶ Drug metabolism tests
- ▶ Our body has an arsenal of metabolic enzymes that can modify foreign chemicals in such a way that they are rapidly excreted.
- ▶ The structures formed from these reactions are called drug metabolites.
- ▶ It is important to find out what metabolites are formed from any new drugs.
- ▶ The structure and stereochemistry of each metabolite has to be determined.

Preclinical and clinical tests

- ▶ The metabolites should be tested to see what sorts of biological activity it may have.
- ▶ Some metabolites may be toxic and some may have side effects.
- ▶ It affects the dose levels that can be used in clinical trials.
- ▶ It ideally all metabolites formed are inactive and quickly excreted.
- ▶ In order to study the biological activity, the drug is synthesized with isotopically labelled (e.g. deuterium ^2H , tritium ^3H , carbon 13 ^{13}C , carbon 14 ^{14}C).
- ▶ It takes blood and urine samples for analysis.

Preclinical and clinical tests

- ▶ In vitro drug metabolism test,
- ▶ Using perfused liver system
- ▶ Liver microsomal fractions
- ▶ Pure enzymes

Preclinical and clinical tests

- ▶ Pharmacological test
- ▶ During the drug discovery and drug design stages.
- ▶ Formulation test
- ▶ Checking if it is stable and acceptable to the patient
- ▶ E.g. incorporating the drug into a tablet or a capsule, compatible

Preclinical and clinical tests

- ▶ All pre-formulation characterisation
- ▶ physical, chemical and mechanical properties
- ▶ Particle size, salt forms, crystal polymorphism, solvates, pH, solubility

Preclinical and clinical tests

- ▶ Stability tests
- ▶ It is essential in phase III clinical trial.
- ▶ Temperature
- ▶ Humidity
- ▶ Ultraviolet light
- ▶ Visible light
- ▶ Any degradation products

Preclinical and clinical tests

- ▶ Important
- ▶ Any unwanted interactions between the preparation and the container
- ▶ Any plasticizers, lubricants, pigments, stabilizers leaching out of plastic container into drug preparation

Preclinical and clinical tests

- ▶ Proceed to Clinical tests if
- ▶ desired effect in animal tests,
demonstrates a distinct advantage over established therapies and
acceptable pharmacokinetics,
few metabolites,
a reasonable half-life,
no serious side effects.

Preclinical and clinical tests

Phase I	Phase II	Phase III
One year 100-200 volunteers	Two years Patients	Three years
Drug safety Pharmacokinetics Different dose	II(a) and II(b) Pharmacokinetics Short-term safety Best dose regimen	III(a) and III(b) Effectiveness Beneficial effects
Active drug Placebo (安慰劑)	Double-blind Placebo-controlled	Double-blind (larger sample of patients)

Preclinical and clinical tests

- ▶ Phase IV
- ▶ The drug is now placed on the market and can be prescribed.
- ▶ It stills under monitoring for effectiveness and any rare or unexpected side effects
- ▶ A never-ending process
- ▶ As unexpected side effects may crop up many years after the introduction of the drug in the market.

Manufacturing of the tablets

- ▶ Dispensing
- ▶ Sizing
- ▶ Powder blending
- ▶ Granulation (wet granulation; dry granulation)
- ▶ Drying
- ▶ Tablet compression

Dispensing

- ▶ Dispensing is the first step in any pharmaceutical manufacturing process.
- ▶ It is one of the most critical steps in pharmaceutical manufacturing.
- ▶ During the step, the weight of each ingredient in the mixture is determined according to the dose.

Sizing

- ▶ The sizing is an important step in the process of tablet manufacturing.
- ▶ Size reduction
- ▶ Milling
- ▶ Crushing
- ▶ Grinding
- ▶ Pulverization
- ▶ The mixing or blending of several solid pharmaceutical ingredients is easier and more uniform if the ingredients are about the same size.

Powder blending

- ▶ The successful mixing of powder is more difficult than mixing liquid as perfect homogeneity is difficult to achieve.
- ▶ This arises from the difference in size, shape, and density of the component particles.
- ▶ The optimum mixing time and mixing speed must be evaluated.

Granulation

- ▶ Following particle size reduction and blending, the formulation may be granulated, it provides homogeneity of drug distribution in blend.
- ▶ The process is very important.
- ▶ If granulation is not done in a proper manner, the resulting mixture may damage the tableting press.

Drying

- ▶ Drying is an important step in the formulation and development of a pharmaceutical product.
- ▶ It is important to keep the residual moisture low enough to prevent product deterioration and ensure free flowing properties.

Tablet Compression

- ▶ After the preparation of granules or sized or mixing of ingredients, they are compressed to get final product.
- ▶ The compression is done either by single punch machine or multi station machine.
- ▶ It can make the tablet in many shapes although they are usually round or oval.
- ▶ There is also direct compression.

Quality Control of Tablets

Quality Control of Tablets

- ▶ Apparent features of tablets
- ▶ E.g. color, shape, diameter, etc.
- ▶ Tablets must meet other physical specifications and quality standards.
- ▶ Include criteria for weight, weight variation, content, uniformity, thickness, hardness, disintegration, and dissolution.
- ▶ Must be controlled during production (in-process controls) and verified after the production of each batch by QC tests.
- ▶ To ensure established product quality standards are met.

Manufacture of Tablets

- ▶ Choice of manufacturing process depends on several factors
 - ▶ The compression and flow properties of the active ingredients and excipients
 - ▶ The excipients used to formulate the product
 - ▶ The particle size of the active ingredients and excipients
 - ▶ The physical and chemical stability of the active ingredients during the manufacturing process
 - ▶ The availability of the necessary processing equipment
 - ▶ The cost of the manufacturing process

Quality Control of Tablets

Official QC tests (Compendial Tests)

- ▶ British Pharmacopoeia (BP) and US Pharmacopoeia (USP)
 - ▶ Uniformity of active ingredient content
 - ▶ (Uniformity of weight and content uniformity)
 - ▶ Disintegration test
 - ▶ Dissolution test
 - ▶ Friability test

Quality Control of Tablets

Disintegration Test

- ▶ Test is carried out by
- ▶ Agitating a given number of tablets (i.e. 18) in an aqueous medium (i.e. H₂O / simulated gastric fluid) at a defined temperature (37°C) and the time to reach the end point of the test is recorded.
- ▶ The requirements for disintegration test are met if the time to reach this end point is below given limit (i.e. 15-30 minutes for uncoated immediate release tablets).

Quality Control of Tablets

Dissolution Test

- ▶ An important tool to assess factors that affect the bioavailability of a drug from a solid dosage form.
- ▶ Dissolution tests are carried out for several reasons:
 - ▶ To evaluate the possible effect of formulation and process variables on the bioavailability of a drug
 - ▶ To indicate the performance of the tablet produced under in vivo conditions

Quality Control of Tablets

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 - ▶ To evaluate the possible effect of formulation and process variables on the bioavailability of a drug
 - ▶ To indicate the performance of the tablet produced under in vivo conditions
- ▶ The requirements for dissolution test are met if not $< 75\text{-}80\%$ of the amount of drug labelled dissolved within 30-45 minutes, according to the parameters described in the individual monograph.

Quality Control of Tablets

Hardness and Friability Test

- ▶ Hardness – In general, tablets should be sufficiently hard to resist breaking during normal handling, packaging and shipping, and yet soft enough to disintegrate properly after swallowing.
 - ▶ An important criterion, since it can affect disintegration and dissolution of the tablets
- ▶ Hardness – It is controlled by (or is affected by the degree of the pressure applied during the compression stage.
- ▶ Friability – The tendency of the tablet to crumble.
 - ▶ It is important for the tablet to resist of attrition (摩擦).
- ▶ Friability – It is determined by weighting before and after a specified number of rotations in a friabilator and any weight loss is determined.

Quality Control of Tablets

Hardness and Friability Test

- ▶ The requirements for friability test are met if a maximum loss of not $> 1\%$ of their weight are generally considered acceptable for conventional compressed tablets.
- ▶ Resistance to loss of weight indicates the tablet's ability to withstand abrasion in handling, packaging and shipment.

Quality Control of Tablets

Non-compendial Tests

- ▶ Many tests are frequently applied to tablets for which there are non-pharmacopoeial requirements but will form a part of manufacturer's own product specifications.
 - ▶ Tablet thickness
 - ▶ Tablet hardness

Quality Control of Tablets

Quality Control of Tablets

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